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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/535,581	01/17/2006	Thomas Link	23062	7537

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EXAMINER	
BARNHART, LORA ELIZABETH	
ART UNIT	PAPER NUMBER
1651	

MAIL DATE	DELIVERY MODE
06/10/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/535,581	LINK ET AL.	
	Examiner	Art Unit	
	Lora E. Barnhart	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 March 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28 and 29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28 and 29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendments

Applicant's amendments filed 3/17/10 to claim 28 have been entered. No claims have been canceled or added. Claims 28 and 29 remain pending in the current application and are being considered on their merits. References not included with this Office action can be found in a prior action. Any rejections of record not particularly addressed below are withdrawn in light of the claim amendments and applicant's comments.

Election/Restrictions

Applicant's election with traverse of the species "CHO cells" and "immunoglobulins" in the reply filed on 5/13/08 is still in effect over the claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 28 and 29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 28 has been amended to require that the "constant flow rate" of the glucose solution being fed into the cell-containing media is from "D = 0.03/h to D = 0.05/h, but D is defined as "volume flow of the media per hour divided by total media volume." The definition of "D" within the claim is confusing because it refers to "media flow rate" and "media volume," but the glucose added at this rate is referred to as a

"solution" or a "feed." The term "media" refers elsewhere in the claim (step a) to a composition containing cells. It is not clear whether this "media flow rate" refers to the "media" or to the glucose "solution feed." Clarification is required.

Because claim 29 depends from indefinite claim 28 and does not clarify the point of confusion, it must also be rejected under 35 U.S.C. 112, second paragraph.

Applicant's comments regarding the rejections of record have been considered, but they are not persuasive. Applicant indicates that D refers to "the volume flux of the feed added to the vessel," referring to "paragraph 38 of the specification." First, the as-filed specification contains no paragraph numbers; applicant was requested to refer to the as-filed specification. See 12/18/09 Office action, page 9. Second, as described above, the claims do not clearly indicate that D refers to the "volume flux of the feed added to the vessel," since they define D in terms of "media." Finally, paragraph 38 of the pre-grant publication (presumably the "paragraph 38" to which applicants refer) does not clarify the problem since it merely recites the term "media flow rate (D)."

Claims 28 and 29 rejected under 35 U.S.C. 112, second paragraph, as failing to set forth the subject matter which applicant(s) regard as their invention. Evidence that claims 28 and 29 fail to correspond in scope with that which applicant(s) regard as the invention can be found in the reply filed 3/17/10. In that paper, applicant has stated that "D" in claim 28 refers to "the volume flux of feed added to the vessel." See reply, page 5, paragraph 3. This statement indicates that the invention is different from what is defined in the claim(s) because the claims define D in terms of "media flow rate," where

"media" is employed in an earlier step as referring to the composition within a culture vessel that contains cells; the glucose solution is not a "media."

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 28 and 29 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Folena-Wasserman et al. (1993, U.S. Patent 5,252,216) taken in view of Keen et al. (1994, U.S. Patent 5,316,938).

Folena-Wasserman teaches a method for producing a recombinant protein comprising culturing CHO cells in a mixture of DMEM and Ham's F-12 medium until the cells reach a critical concentration, then perfusing glucose into the culture at a constant rate such that the glucose concentration within the culture remains at 1.0g/L (i.e., 6

mmol/L, which is "about 24 mmol/L"), and then recovering the recombinant protein. See column 11, line 41, through column 12, line 46. Folena-Wasserman teaches that the method may be used to produce virtually any recombinant protein. See column 12, lines 47-58.

Folena-Wasserman does not specifically teach producing antibodies. Folena-Wasserman does not exemplify an embodiment in which glucose is added once the cell count reaches $1.8x10^6$ cells/mL medium or one in which the glucose level is higher than 1.0 g/L (6 mmol/L).

Keen teaches a method for producing Campath 1H human IgG antibody from recombinant CHO cells comprising culturing the cells in serum-free WCM4 medium, which contains 4.5g glucose/L (25 mmol/L), at pH 6.5-7.5 and recovering the secreted antibody. See example 3 at column 8; Table 1 at columns 4-5; and column 3, lines 30-40. Keen teaches that the medium can support cells at a density up to or greater than $1.5x10^6$ cells/mL. See column 6, lines 44-55, and line 38 of Table 3 at column 11. Keen teaches that any antibody can be produced using the medium. See column 6, line 56 et seq.

A person of ordinary skill in the art would have had a reasonable expectation of success in substituting the recombinant cells and medium of Keen for the cells and medium of Folena-Wasserman in the method of Folena-Wasserman because the cited references establish that both are useful for producing recombinant proteins. The skilled artisan would have been motivated to make this substitution in order to yield antibodies, which are therapeutically useful.

The selection of the concentration of cells in the medium at the time of glucose addition would have been a routine matter of optimization on the part of the artisan of ordinary skill, said artisan recognizing that Folena-Wasserman teaches waiting to add glucose until the cell density reaches a critical point and that Keen's medium can support growth of cells at the claimed high density. A holding of obviousness over the cited claims is therefore clearly required.

The selection of the concentration of glucose in the medium would have been a routine matter of optimization on the part of the artisan of ordinary skill, said artisan recognizing that Folena-Wasserman and Keen teach that CHO cells produce recombinant proteins at 1.0-4.5g glucose/L (i.e., 6-25 mmol/L). A holding of obviousness over the cited claims is therefore clearly required.

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the method of Folena-Wasserman to use the antibody-producing cells, medium, high glucose concentration, and high cell density of Keen in order to produce antibodies because Folena-Wasserman's method produces high levels of recombinant protein and Keen's system produces high levels of antibodies specifically.

Therefore, the invention as a whole would have been *prima facie* obvious to a person of ordinary skill at the time the invention was made.

Applicant alleges that Folena-Wasserman's teaching "periodic increases in feeding rates" distinguishes the claims over the prior art. See reply, page 6, paragraph 2. Applicant alleges that the instant claims require that the feed be kept constant and

that the glucose concentration within the culture vessel decreases. See reply, page 6, paragraph 3. Applicant alleges that the D value must be kept constant. See reply, page 6, paragraph 4. These arguments have been fully considered, but they are not persuasive.

At column 11, line 68, Folena-Wasserman teaches "periodic increases in rate," which reasonably means that the feed solution is perfused first at one rate, then increased as necessary to a higher rate. Folena-Wasserman teaches "initiating medium perfusion . . . at a rate sufficient to maintain the glucose concentration." See column 12, lines 15-17. Any time the rate is not being increased (or decreased), it is "constant." The instant claims do not require that the flow rate be constant throughout the process, all that they require is that the method comprise "starting feeding of glucose at a constant flow rate." The transitional phrase "comprising" opens the claim to include additional, unrecited process steps (e.g., a later increase or decrease in rate to yield a second constant rate, as taught by Folena-Wasserman). There is no requirement in the claims that "the glucose concentration inside the reaction vessel is not kept constant," as applicant alleges at page 6, paragraph 3; limitations from tables within the specification cannot be incorporated into the claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). The claims also do not require that the feed rate be kept constant throughout the method; they specifically allow that D, the media flow rate, may vary from 0.03/h to 0.05/h.

No claims are allowed. No claims are free of the art.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lora E. Barnhart whose telephone number is (571)272-1928. The examiner can normally be reached on Monday-Thursday, 9:00am - 5:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lora E Barnhart/
Primary Examiner, Art Unit 1651